Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 215-292 are pending in the application, with 215, 231, 245, 261 and 275 being the independent claims. Claims 136-214 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 215-292 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Support for new claims 215-292 may be found in the specification, *inter alia*, at the following paragraphs: [0015], [0017], [0087], [0089], [0090] [0094], [0116], [0277], the abstract and the claims as originally filed.

Applicant notes the Examiner's comment that variants and fragments of SEQ ID NO:4 (SEQ ID NOs: 2, 6 and 8) would be examined as long as they depend from an elected claim. Thus, in order for the claims to correctly depend from one another, Applicant has added new independent claims 215, 231, 245, 261 and 275 which include the anthrax protective antigen (PA) polypeptide sequence contained in SEQ ID NO:2 (amino acids 199 to 764 of SEQ ID NO:4). Dependent claims 216, 232, 246, 262 and 276 include the PA polypeptide sequence contained in SEQ ID NO:6 (199-764 of SEQ ID NO:4 with amino acids 342 and 343 deleted). Dependent claims 220, 236, 250, 266, and 280 include the PA polypeptide sequence contained in SEQ ID NO:8 (30-764 of SEQ ID NO:4 with amino acids 192-197 deleted).

Statement of Substance of Interview

Pursuant to 37 C.F.R. § 1.133, Applicant provides the following statement of Substance of the Interview. Applicant wishes to thank Examiners Singh and Woitach for the courtesy of an interview with Applicant's representatives on September 5, 2006. Rejections of record were discussed in view of the proposed claim amendments. It was agreed upon that Applicant would add composition claims which parallel the method claims. Amendments, as discussed, are filed herewith.

Objection to the Claims

The Examiner has objected to claim 174 as it was dependent on claims directed to non-elected subject matter. Applicant has cancelled claim 174 and added new claims 215-292. As such, Applicant believes the Examiner's objection to be moot.

Rejections under 35 U.S.C. § 112, 1st Paragraph (Enablement)

Claims 139, 151 and 174 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. *See* Office Action, page 4. Applicants respectfully traverse this rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

According to the Examiner, the specification allegedly does provide enabling disclosure for the claimed method as the specification allegedly does not provide

guidance in treating any form of anthrax by administering via any route a plurality of polynucleotides in any formulation which when expressed resulted in an immune response sufficient to treat or prevent any form of anthrax. *See* Office Action, page 6. Applicant respectfully disagrees.

First, the Examiner alleges that it is not apparent whether a sequence with 90% identity to SEQ ID NO:4, that is optimized for humans, would elicit an effective immune response against anthrax. *See* Office Action, page 8. The Examiner asserts that the artisan practicing the invention would have to carry out undue experimentation as "only optimal codon usage would have provided optimal immune response sufficient for the treatment of *Bacillus anthracia* infection." *See* Office Action, page 8. The Examiner cites Nagata *et al.* in support of the proposition that only optimal codon usage elicits an effective immune response. *See* Office Action, page 8.

Applicant asserts that the claimed methods do not require any specific level of immune response other than to treat or prevent anthrax infection as defined in the specification, *e.g.* at paragraphs [0057] and [0116]. Certainly, the claimed methods do not require an "optimal immune" response as the examiner is requiring. The data in the Nagata *et al.* reference showed some level of immune response in all DNA plasmids tested, including the plasmid which had the native codon usage. *See* Fig. 3. Moreover, Applicant asserts that based on the teaching in the specification, it would have been routine experimentation for one of skill in the art to test various codon optimized polynucleotides in the mouse, rabbit and primate animal models described in Examples 10-13 and 15 or in the assays described in Example 9 of the present application to determine which variants could treat or prevent anthrax infection.

Solely in an effort to advance prosecution, and not acquiesing in the propriety of the rejecetion, Applicant has added new independent claims 215, 231, 245, 261 and 275, from which all other claims depend, which recite "an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4." Applicant asserts that the claimed percent identity allows for variation in the amino acid sequence of the protective antigen polypeptide among strains of *B. anthracis*. Applicant provides herewith, as Exhibit A, the following reference: Price *et al.*, "Genetic Diversity in the Protective Antigen Gene of *Bacillus anthracis*." *J. of Bacteriology* 181:2358-2362 (1999) (previously submitted in an IDS filed August 26, 2005 as document number **NPL2**). The Price *et al.* reference discusses variation in the protective antigen gene among 26 strains of *B. anthracis*. As some variability exists, Applicant asserts that 97% identity with respect to the polypeptide would allow for the use of the protective antigen in the claimed invention from various strains of *B. anthracis*, and further encompasses deletion analogous to those specifically disclosed in the specification .

The Examiner also alleges that the claims are not enabled for administration of a polynucleotide via any route of administration to elicit an immune response. *See* Office Action, page 9. The Examiner argues that the specification does not provide any specific guidance to overcome the unpredictability recognized in the art for various considerations in treating or preventing anthrax infections with DNA vaccines such as: (1) dosing; (2) the type and route of anthrax infection; and (3) the levels of antibody optimal for protection or treatment in any subject. *See* Office Action, page 11.

The Examiner cites Galloway *et al.* for the proposed notion that the field of DNA vaccines is a largely unpredictable and experimental field and although progress has been made in the field of DNA vaccines, the desired immune response produced by DNA vaccines continue to be unpredictable and inefficient. *See* Office Action, page 9. Additionally, the Examiner cites Leppla *et al.* to support his allegation that there are a number of uncertainties as to what would be the optimal concentration of serum antibodies in humans which would confer immunity to anthrax. *See* Office Action, page 10. Finally, the Examiner alleges that treatment of anthrax by a recombinant vaccine is unpredictable as there are remaining questions regarding the efficacy of a anthrax DNA vaccine in human patients. *See* Office Action, page 10.

Applicant respectfully asserts that the Examiner is requiring an unreasonable enablement standard. The Federal Circuit has stated that the PTO has the burden of initially showing that Applicants' disclosure suggests "an inherently unbelievable undertaking or involve[s] implausible scientific principles." *In re Brana*, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995). The documents cited by the Examiner do not meet this burden.

Applicant notes that the Galloway *et al.* reference, cited by the Examiner to show the unpredictability of DNA vaccines, comments on the success of DNA vaccines currently in clincal trials. "A number of DNA vaccines are undergoing Phase I and IIa human trials at present, involving hundreds of human volunteers and so far have demonstrated that DNA vaccines are safe, well tolerated and capable of inducing both humoral and cellular immune responses." Galloway and Baillie, *Expert Opin. Biol. Ther.*, 4:1661-67, (2004) at page 1663. Additionally, Galloway states that "[t]he

effectiveness of ballistic delivery (gene gun) and cationic lipid formulations suggests that it is indeed possible to develop modalities that ***ensure*** efficient DNA uptake and effectively stimulate the primate immune response. Galloway at page 1665 (emphasis added).

Furthermore, the Leppla reference provides no data which disproves or calls into question the enablement of Applicant's invention. Leppla *et al.* presents technical issues to be considered when developing an anthrax vaccine, however, these issues do not mean that claimed invention is unpredictable or not enabled.

Applicant respectfully reminds the Examiner that the proper standard for compliance with enablement is not *absolute predictability* but *objective enablement*; evidence need not be *conclusive* but merely *convincing*. Accordingly, Applicant submits that the compelling animal data presented in the specification is sufficiently convincing that one of ordinary skill in the art would not doubt the feasibility of the claimed invention. Moreover, the *in vivo* successes documented in the Examples of the instant specification, *e.g.* Examples 10-13, clearly outweigh any speculative allegations of unpredictability asserted by the Examiner.

According to the Examiner's apparent view of the enablement requirement, an applicant would have to submit conclusive data from human clinical trials in order to adequately enable a method of treatment applicable to humans. This is clearly in conflict with the statute, the rules and the guidelines of the M.P.E.P. Specifically, under the current case law, clinical efficacy is not required to show that a therapeutic process is operable. As stated in M.P.E.P. § 2107.01, the "courts have found utility for therapeutic inventions, despite the fact that an applicant is at a very early stage in the development of

a therapeutic regimen" or that a therapeutic treatment regimen is not at a stage where it is ready to be practiced on humans. *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985); *In re Brana*, 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

It is not within the province of the USPTO to require proof of efficacy in animals to grant a patent including claims to therapeutic methods. The PTO guidelines, in fact are explicit on this point: "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." (M.P.E.P. § 2107.03). The guidelines further state that "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law, and in quoting *In re Brana*, *supra*, that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws". *Id.* In fact, all that is required by the patent laws is that a "*reasonable correlation*" exist between the scope of the claims and the scope of enablement. Citing to M.P.E.P. § 2164.02, "'correlation' as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." If a particular model is recognized as correlating to a specific condition, then it should be accepted as such unless the Examiner has evidence that the model does not correlate. *In re Brana, supra* at 1566. Since the initial burden is on the Examiner to give reasons for lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. As stated in *Cross v. Iizuka*, *supra*, at 1050, a rigorous or an invariable exact correlation is not required.

The references cited by the Examiner and arguments set forth do not cast doubt on the feasibility of the claimed invention in light of the data presented in the specification. Indeed, the captioned application describes various *in vitro* assays known in the art which sufficiently correlate to *in vivo* anthrax challenge experiments, *e.g.* at paragraph [0155] of the specification. The specification also describes data for various vaccine compositions in three different animal models. *See* Examples 10-13 and 15. Furthermore, the captioned application contains data showing that DNA vaccines containing codon optimized polynucleotides encoding anthrax antigens can provide protective immunity in rabbits. *See* Example 13. Finally, post-filing art, co-authored by the inventor of the captioned application, reports that the rabbit studies described herein resulted in product selection, pre-clinical safety studies, and U.S. FDA Investigational New Drug allowance. *See* Hermanson, *et al.* "A cationic lipid-formulated plasmid DNA vaccine confers sustained antibody-mediated protection against aerosolized anthrax spores." *Proc. Natl. Acad. Sci.* 101:13601-13606, 1306 (2004) (Exhibit B) (previously submitted in an IDS filed August 26, 2005, as document number **NPL4**). Applicant asserts that a reasonable correlation thus exists between the data provided in the captioned application and the claimed methods.

Not only is the Examiner requiring an enablement standard which is higher than required by the USPTO, but he is setting a standard which is higher than what is required by the FDA. Indeed, to truly determine whether an anthrax vaccine offered protective immunity in humans or even protection against does of 500-5000 LD_{50} in a bioterrorist attack, as the Examiner is suggesting is required (*See* Office Action, page 10), one would have to inoculate a human and then expose them to anthrax. There would be no other

way to determine the effectiveness of a proposed DNA vaccine if, as the Examiner suggests, animal data cannot be relied upon. Clearly exposing humans to anthrax in human clinical trials is highly unethical and is not required by the FDA for approval of an anthrax vaccine. *See* 67 Fed. Reg. 37989 (May 31, 2002) (Exhibit C).

Thus, given the explicit disclosure of specific *in vivo* working examples, using models that reasonably correlate to mammals, as noted in paragraph [0155] of the specification, Applicants respectfully submit that one skilled in the art would be able to make and use the claimed invention without undue experimentation.

The Examiner has also commented that the examples of the specification do not teach all possible variants of SEQ ID NO:4 and do not provide a sample size which provides adequate "power" for determining appropriate immune response, citing Brey *et al., Ann. N.Y. Acad. Sci.* 823:97-106 (1997). *See* Office Action, pages 12-13. Applicant respectfully disagrees.

As the Federal Circuit has held:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). Therefore, the Examiner is again respectfully reminded that the proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.,* 8 USPQ2d 1217,

1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987).

Indeed, one of skill in the art, relying upon the examples in the specification, could test all possible variants of SEQ ID NO:4 claimed to determine the immunogenicity of the polypeptide in the assays and animal models described. The assays described in the examples of the specification are routine to one of skill in the art and as such would not be undue experimentation. Significantly, no evidence has been presented to suggest that such screening would have been considered undue experimentation.

Applicant notes that new independent claims 215, 231, 245, 261 and 275, from which all other claims depend state that the composition comprising the polynucleotide encoding an anthrax polypeptide elicits an immune response directed to the anthrax polypeptide. As such polynucleotides encoding polypeptide variants could be screened for the claimed activities by one of skill in the art without undue experimentation using the assays described in the captioned application.

Additionally, Applicant disagrees with the Examiner that the sample size used in the immunization experiments of the specification are too small to be significant. The Examiner is again reminded that the proper standard for compliance with enablement is *convincing* evidence not *conclusive* evidence. Furthermore, the PTO guidelines state that proof of efficacy in animals is not required to grant a patent with claims to therapeutic methods.

Examples 12 and 13 of the captioned application describe immunization and challenge experiments in 12 groups of rabbits (10 rabbits in each group) and one group

of 4 rabbits (which were immunized with the commercial AVA anthrax vaccine). This is a total sample size of 124 animals, with 10 animals per formulation. Indeed, all animals which were immunized with SEQ ID NO:8 and Vaxfectin or DMRIE/DOPE survived anthrax spore challenge as described in Table 17. Thus, despite the Examiner's comments regarding variability in neutralizing data and the small sample size of 8-10 animals (*See* Office Action, page 13), Applicant has shown that immunization with an anthrax DNA vaccine can provide protective immunity in at least 40 animals. *See* Table 17. Additionally, the animals tested were subjected to aerosolized anthrax spore challenge which is "the gold standard for anthrax vaccine efficiency because it exposes the animal to the agent and expected mode of delivery anticipated in the event of a bioterrorist attack." Hermanson, *et al.* "A cationic lipid-formulated plasmid DNA vaccine confers sustained antibody-mediated protection against aerosolized anthrax spores." *Proc. Natl. Acad. Sci.* 101:13601-13606 (2004) (Exhibit B).

The Examiner also sets forth the argument that it would be undue experimentation for one of skill in the art to formulate the DNA vaccine of the claimed invention in any type of lipid due to the influence of the lipid on the immunogenic response, pharmacokinetics and biodistribution of the DNA vaccine. Applicant respectfully disagrees.

The Examiner cites Jones *et al.* in support of the notion that micelle composition influences the "zeta potential on the pharmacokinetics, biodistribution and ability of the carried drug." Jones *et al.* at page 109. However, the reference is directed to the use of micelles in the delivery of poorly water soluble and amphiphilic drugs, not DNA which

is used in the methods of the claimed invention. As such, it is unclear how this reference relates to the enablement of the present invention.

Formulation of a DNA molecule with various lipids is routine to one of skill in the art and is described in the specification. Specifically, Examples 11 and 12 describe immunization of mice and rabbits with various DNA vaccine formulations, for example CRL 1005/BAK; Vaxfectin; and DMRIE:DOPE. As such it would not be undue experimentation for one of skill in the art to test other formulations. Indeed, Perrie *et al.*, cited by the Examiner, states that

> [r]esults indicate much greater fluorescence intensity (presumably reflecting greater expression of enhanced green fluorescent protein) in both the injected muscle and the draining popliteal and inguinal lymph nodes of mice treated with the liposomal plasmid than in the animals treated with the same amount of naked plasmid.... Our results indicate that a phospholipid with a low Tc combined with the fusogenic DOPE (or PE) and an appropriate surface charge (or zeta potential) contributes to ***optimal immune*** responses to the antigen encoded by the liposome-entrapped pRc/CMV HBS plasmid.

Perrier *et al.*, page 3308 (emphasis added). Again the Examiner is reminded that the claims do not require an optimal immune response. As stated above, the examples of the specification show that SEQ ID NO:8 and at least two different types of lipid formulations result in protective immunity against anthrax challenge.

The Examiner also cites Dass for the proposition that lipoplex-mediated gene delivery can be toxic. *See* Office Action, page 15. Applicant disagrees and provides herewith a post filing reference, co-authored by the inventor, (Ferrari *et al.*, "Development of anthrax DNA vaccines." *Curr. Op. in Mol. Therap.* 6:506-512 (2004) (Exhibit D)) which summarizes various published studies using DNA vaccines

formulated with various lipids. Table 1 lists 18 different studies with various antigens and 11 different lipid formulations. Thus, Applicant asserts that lipid formulated vaccines are not toxic and useful in DNA vaccines. Indeed the Ferrari *et al.* reference states that "there is extensive preclinical evidence suggesting that cationic lipid-based formulations significantly enhance humoral responses of DNA vaccines." Ferrari *et al.*, page 508-9.

Finally, the Examiner makes several unsupported claims regarding the predictability of transduced therapeutic genes *in vivo* due to target cell type, vector selection and administration. *See* Office Action, page 13. However, these statements are purely speculative and the Examiner has provided no evidence in support of his assertions.

For the reasons given above, Applicant submits that the scope of the present claims is commensurate in scope with the enablement provided in the present specification. The considerations listed by the Examiner are either resolved by the teachings in the specification or would have required only routine experimentation by one of skill in the art to practice the claimed invention. Accordingly, Applicant requests reconsideration and withdrawal of the enablement rejection in view of the amendments to the claims and the remarks herein.

Rejections under 35 U.S.C. § 112, 2nd Paragraph

The Examiner has rejected claim 174 under 35 U.S.C. § 112, 2nd paragraph as allegedly being incomplete for omitting essential steps. *See* Office Action, page 16. Applicant respectfully traverses.

The Examiner alleges that the claim recites a method without any active step on how the claimed method will be practiced. Applicant respectfully disagrees and asserts that cancelled claim 174, as well as new method claims 215-274 presented herein, recite active steps. For example, new claim 215 recites "administering to a vertebrate in need thereof a composition". Additionally, the Examiner states that it is unclear what method the Applicant is intending to encompass. Applicant respectfully disagree and assert that the claims are directed to a method of treating or preventing anthrax infection or inducing an immune response to anthrax via administration to a vertebrate of a specific polynucleotide encoding a codon optimized anthrax antigen.

Solely in an attempt to expedite prosecution, and not acquiescing in the propriety of the rejection, Applicant has added new independent claims 215, 231, 245 and 261 from which all other method claims depend. The new independent claims recite the active step of "wherein said composition elicits an immune response to said polypeptide." Based on the amendments to the claims and arguments above, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 102(e)

The Examiner has rejected claims 139, 151 and 174 under 35 U.S.C. § 102(e) as allegedly being anticipated by Lee *et al.* U.S. Patent Application Publication No. 2004/0009945 ("Lee *et al.*"). *See* Office Action, page 17. Applicant respectfully disagrees.

Solely in an attempt to expedite prosecution, and not acquiescing in the propriety of the rejection, Applicant has cancelled claim 174 and provide herewith new claims 215-292. Independent claims 215, 231, 245 and 261, from which all other method

claims depend, recite a method for treating or preventing anthrax infection in a vertebrate "comprising administering to a vertebrate in need thereof a composition comprising a carrier, [a lipid GAP-DMORIE or DMRIE], a co-lipid and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4." Applicant asserts that Lee *et al.* does not disclose the administration of a polynucleotide encoding a polypeptide at least 97% identical and codon optimized, as set forth in independent claims 215, 231, 245, 261 and 275, in combination with the lipid GAP-DMORIE or DMRIE and a co-lipid nor does Lee *et al.* disclose the specific codon optimization recited in the claims. As such, Lee *et al.* does not disclose each and every element of the claimed invention as is required for a proper rejection under 35 § 102(e). Thus, Applicant respectfully requests that the Examiner withdraw the rejection as it applies to the currently pending claims.

Rejections under 35 U.S.C. § 103(a)

The Examiner has rejected claims 139 and 151 under 35 U.S.C. § 103(a) for allegedly being obvious over Lee *et al.* or Katritch *et al.*, U.S. Patent Application Publication No. 2003/0235818 ("Katrich *et al.*") or Collier *et al.*, U.S. Patent Application Publication No. 2002/0039588 ("Collier *et al.*") in view of Nagata *et al.*, *Biochem. Biophys. Res. Commun.* 261:445-51 (1999) ("Nagata *et al.*"). *See* Office Action, pages 18-19. Applicant respectfully traverses.

In order to support a *prima facie* case of obviousness, the prior art must suggest making the *specific* molecular modifications necessary to achieve the claimed invention. *See In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984) ("[t]he prior art must provide one of ordinary skill in the art the

motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). That is, simply because "one can conceive a general process in advance for preparing an *undefined* compound [*e.g.*, a codon optimized polynucleotide encoding the protective antigen of *B. anthracis*] does not mean that a claimed *specific* compound [*e.g.*, a polynucleotide encoding a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4 which has been codon optimized in a manner specified in independent claims 215, 231, 245, 261 and 275] was precisely envisioned and therefore obvious." *Deuel* at 1559. Thus, in order for cited references to be suitable as primary references upon which to base a *prima facie* case of obviousness, there must be, at a minimum, a teaching or suggestion in these references that would have compelled one of ordinary skill in the art to codon optimize a polynucleotide encoding SEQ ID NO:4 as claimed. Especially in view of the numerous potential polynucleotides which could encode for SEQ ID NO:4 and the numerous potential ways to codon optimize the polynucleotides. Therefore, the cited references taken together are seriously deficient (particularly in view of the holding in *Deuel*), and cannot support a *prima facie* case of obviousness.

Solely in an attempt to expedite prosecution, and not acquiescing in the propriety of the rejection, Applicant has cancelled claim 174 and provide herewith new claims 215-292. Independent claims 215, 231, 245 and 261, from which all other method claims depend, recite a method for treating or preventing anthrax infection in a vertebrate "comprising administering to a vertebrate in need thereof a composition comprising a carrier, [a lipid GAP-DMORIE or DMRIE], a co-lipid and an isolated polynucleotide comprising a nucleic acid fragment which encodes a polypeptide at least 97% identical to

amino acids 199 to 764 of SEQ ID NO:4." Applicant asserts that neither Lee *et al.*, Katrich *et al.*, nor Collier *et al.* teach or suggest the administration of a polynucleotide encoding a polypeptide at least 97% identical to amino acids 199 to 764 of SEQ ID NO:4 and codon optimized, as set forth in claims 215, 231, 245, 261 and 275, in combination with the lipid GAP-DMORIE or DMRIE and a co-lipid nor do they suggest or disclose the specific codon optimization recited in the claims.

Nagata *et al.* does not cure the deficiencies of Lee *et al.*, Katrich *et al.*, or Collier *et al.* Indeed, Nagata *et al.* discloses the use of a gene encoding amino acid residues 91 to 99 of listeriolysin O (LLO) derived from *Listeria monocytogenes*. The gene was codon optimized for mouse and then used to immunize mice via the gene-gun delivery method. Nagata *et al.* does not teach or suggest the administration of a codon-optimized polynucleotide encoding a polypeptide at least 97% identical to SEQ ID NO:4 administered to a vertebrate in a composition comprising GAP-DMORIE or DMRIE and a co-lipid as claimed.

As such, the combined references cited by the Examiner do not teach or suggest the claimed methods, let alone provide motivation for the combination or a reasonable expectation of success. Therefore, Applicant respectfully requests withdrawal of the rejection as it relates to the currently pending claims.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Elizabeth J. Haanes, Ph.D.
Attorney for Applicant
Registration No. 42,613

Date: September 11, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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